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COMMENTARY

Methodological advances to mitigate some of the challenges of research on alcohol and all-cause mortality: Commentary on Rehm

We read Professor Rehm's commentary, which highlights important issues on exposure misclassification, choice of outcome, sampling methods and attrition that complicate attempts to elucidate the true relationship between levels of alcohol use and mortality, with interest [1]. Many of these problems are not unique to alcohol research and apply to many areas of epidemiological enquiry. There are several approaches that can be used to mitigate the impact of these issues and here we outline some of them.

First, all-cause mortality is the outcome of choice for many epidemiological studies. We support Rehm's suggestion that there are difficulties with the interpretation of results from such studies and it has been advised before that studies of all-cause mortality should 'proceed with caution' [2]. Alcohol exposure is associated with many different causes of death [3], each of which may be explained by different causal pathways, may differ in the strength of their relationship with alcohol exposure, and may be subject to different confounding structures. Therefore, it is indeed preferable to use cause-specific mortality risk functions over those for all cause-mortality. However, we would add that even within apparently cause-specific subtypes of mortality, relationships may be complex. For example a large combined analysis of prospective cohort studies, based on 599 912 participants, described how associations between alcohol use and mortality from a variety of cardiovascular diseases, including myocardial infarction, stroke and heart failure, were characterised by multiple different and sometimes opposing risk functions [4]. Accordingly, we echo Rehm's recommendation that causal inference should be supported by knowledge about plausible biological pathways. To formalise this, we suggest that causal diagram methodology could be used to enable transparency about the nature of proposed causal relationships, assisting with the identification of important confounders and safeguarding against inappropriate adjustment of variables for each exposure-outcome combination [5–7].

Second, although Rehm, correctly, argues that general population cohorts are often not representative of the target population and that sampling frames often

exclude important subgroups, we suggest that contemporary statistical methods can be used to eliminate, or at least significantly mitigate the risk of, drawing biased inferences from such studies. For example, sampling weights could be used to rebalance the sample to make it more representative of the target population. The bias and imprecision introduced by participant drop out can also be minimised using established missing data methods, such as multiple imputation and inverse probability weighting [8,9].

Finally, one of the most pressing issues in research on alcohol and mortality is the risk of bias due to uncontrolled confounding. Many studies have found a J-shaped relationship between alcohol use and mortality, with reduced risk for low-level drinkers [10]. However, in a meta-analysis, Stockwell and colleagues demonstrated that this shape was related to the extent to which confounding was controlled for [11]. We suggest that given the vast number of potential confounders in studies of alcohol use and health outcomes, propensity score weighting or matching methods could offer an efficient and effective way to reduce the risk of bias posed by uncontrolled confounding [12].

In summary, we welcome and support Rehm's warning regarding the challenges that are associated with investigating the effect of alcohol use on all-cause mortality. We hope that Rehm's commentary will help stimulate the application of improved methodologies for research in this field and have proposed some strategies that may help address some of these issues to support improved investigations of the complex relationship between alcohol and mortality.

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